

WHAT IS CLAIMED IS:

1. A method for the treatment of a cardiovascular-related condition, the method comprising administering to a subject susceptible to or afflicted with such condition a first amount of an aldosterone receptor antagonist and a second amount of an anti-obesity agent, wherein the first amount of the aldosterone receptor antagonist and the second amount of the anti-obesity agent together comprise a therapeutically-effective amount of the aldosterone receptor antagonist and anti-obesity agent.

2. The method of Claim 1 wherein the aldosterone receptor antagonist is eplerenone.

3. The method of Claim 2 wherein the eplerenone is administered in a daily dose range from about 1 mg to about 250 mg.

4. The method of Claim 2 wherein the cardiovascular-related condition is selected from the group consisting of coronary artery disease, hypertension, cardiovascular disease, renal dysfunction, liver disease, heart failure, cerebrovascular disease, vascular disease, retinopathy, neuropathy, hyperglycemia, hyperinsulinemia, insulin resistance, edema, endothelial dysfunction, baroreceptor dysfunction, of heart failure, arrhythmia, diastolic dysfunction, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardiac death, myocardial fibrosis, vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, endothelial dysfunction and fibrinoid necrosis of coronary arteries.

5. The method of Claim 4 wherein the cardiovascular-related condition is hypertension.

6. The method of Claim 4 wherein the cardiovascular-related condition is renal dysfunction which is selected from the group consisting of glomerulosclerosis, end-stage renal disease, diabetic nephropathy, reduced renal blood flow, increased glomerular filtration

fraction, proteinuria, decreased glomerular filtration rate, decreased creatinine clearance, microalbuminuria, renal arteriopathy, ischemic lesions, thrombotic lesions, global fibrinoid necrosis, focal thrombosis of glomerular capillaries, swelling and proliferation of intracapillary cells, swelling and proliferation of extracapillary cells, expansion of reticulated mesangial matrix with or without significant hypercellularity, and malignant nephrosclerosis.

7. The method of Claim 4 wherein the cardiovascular-related condition is heart failure.

8. The method of claim 4 wherein the cardiovascular related condition is endothelial dysfunction.

9. The method of claim 4 wherein the cardiovascular related condition is vascular disease.

10. The method of claim 4 wherein the cardiovascular related condition is cerebrovascular disease.

11. The method of claim 10 wherein the cerebrovascular disease is stroke.

12. The method of claim 9 wherein the vascular disease is selected from the group consisting of thrombotic vascular disease, proliferative arteriopathy, atherosclerosis, and decreased vascular compliance.

13. The method of claim 4 wherein the cardiovascular related condition is edema.

14. The method of claim 13 wherein the edema is selected from the group consisting of peripheral tissue edema, hepatic congestion, splenic congestion, liver ascites, respiratory congestion, and lung congestion.

15. The method of claim 4 wherein the cardiovascular related condition is selected from the group consisting of hyperglycemia, hyperinsulinemia, and insulin resistance.

16. The method of claim 15 wherein the cardiovascular related condition is selected from the group consisting of Type I diabetes mellitus, Type II diabetes mellitus, insulin resistance, pre-diabetic state, and metabolic syndrome.

17. The method of claim 4 wherein the cardiovascular related condition is selected from the group consisting of coronary heart disease, hypertension, cardiovascular disease, stroke, and Type II diabetes mellitus.

18. The method of claim 17 wherein the cardiovascular related condition is selected from the group consisting of coronary heart disease, hypertension, heart failure, left ventricular hypertrophy and stroke.

19. The method of claim 1 wherein the aldosterone receptor antagonist is selected from the group consisting of:

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo- γ -lactone, methyl ester, (7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,(7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7) pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo- γ -lactone, (6 β ,7 β ,11 β ,17 β)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt,(7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -actone(6 α ,7 α ,11 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6 α ,7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6 α ,7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 α ,7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, ethyl ester, (7 α ,11 α ,17 α)-; and

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ -lactone, 1-methylethyl ester, (7 α ,11 α ,17 α)-.

20. The method of Claim 1 wherein the anti-obesity agent is selected from the group consisting of gastrointestinal lipase inhibitors, mixed norepinephrine and serotonin reuptake inhibitors, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

21. The method of claim 20 wherein the aldosterone receptor antagonist is eplerenone.

22. The method of Claim 2 wherein the anti-obesity agent is selected from the group consisting of orlistat, sibutramine, and pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

23. The method of Claim 21 wherein the anti-obesity agent is orlistat.

24. The method of Claim 21 wherein the anti-obesity agent is sibutramine.

25. The method of Claim 1 wherein the aldosterone receptor antagonist is spironolactone.

26. The method of Claim 1 wherein the anti-obesity agent is orlistat.

27. The method of Claim 1 wherein the anti-obesity agent is sibutramine.

28. The method of Claim 1 wherein the anti-obesity agent is selected from the group consisting of a ciliary neurotrophic factor or one of its related variants or analogs; an appetite suppressant; a 5-HT-2c receptor agonist; a cannabinoid antagonist; a peptide or nonpeptide agonist of the cholecystokinin-A receptor; a peripherally acting agent that delays gastric emptying and increases satiety; an agonist of GLP-1 receptor; GLP-1s and related analogs; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

29. The method of Claim 28 wherein the aldosterone receptor antagonist is eplerenone.

30. The method of Claim 1 wherein the anti-obesity agent is selected from the group consisting of Axokine, CP-644673/P-57, BVT-933, Rimonabant/SR-141716, GI-181771, HMR-1426, and Exendin-4.

31. The method of Claim 30 wherein the aldosterone receptor antagonist is eplerenone.

32. The method of Claim 1 wherein the anti-obesity agent is selected from the group consisting of human growth hormone fragments; PTP-1B inhibitors; DPP-IV inhibitors; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

33. The method of Claim 32 wherein the aldosterone receptor antagonist is

eplerenone.

34. The method of Claim 1 wherein the anti-obesity agent is selected from the group consisting of neuropeptide Y1 antagonists; neuropeptide Y5 antagonists; thyroid hormone receptor beta agonists; glucocorticoid antagonists; melanocortin-4 receptor (MC-4) agonists; adiponectin/APM1/acrp30 and related analogs; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

35. The method of Claim 34 wherein the aldosterone receptor antagonist is eplerenone.

36. The method of Claim 1 the anti-obesity agent is selected from the group consisting of 11-beta-hydroxysteroid dehydrogenase-1 inhibitors; fatty acid synthase inhibitors; acetyl CoA carboxylase inhibitors, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

37. The method of Claim 36 wherein the aldosterone receptor antagonist is eplerenone.

38. The method of Claim 1 wherein the aldosterone receptor antagonist and the anti-obesity agent are administered in a sequential manner.

39. The method of Claim 1 wherein the aldosterone receptor antagonist and the neutral endopeptidase inhibitor are administered in a substantially simultaneous manner.

40. The method of Claim 1 wherein the aldosterone receptor antagonist is administered in a daily dose ranging from about 0.1 to about 2000 mg, and the anti-obesity agent is administered in a daily dose ranging from about 0.1 to about 1000 mg.

41. The method of claim 40 wherein the aldosterone receptor antagonist is eplerenone.

42. The method of claim 41 wherein the eplerenone is provided in a daily dose ranging from about 1 to about 250 mg.

43. The method of Claim 1 wherein the first amount of the aldosterone receptor antagonist produces no substantial diuretic or anti-hypertensive effect in a subject.

44. The method of Claim 1 further comprising administering a third amount of a compound selected from the group consisting of anti-diabetic agents, renin inhibitors, angiotensin I antagonists, angiotensin II antagonists, angiotensin converting enzyme inhibitors, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, calcium channel blockers, endothelin receptor antagonists, endothelin converting enzymes, vasodilators, diuretics, cyclooxygenase-2 inhibitors, apical sodium bile acid transport inhibitors, cholesterol absorption inhibitors, fibrates, niacin, statins, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, anti-oxidants, vitamin E, probucol, IIb/IIIa antagonists, xemilofiban, and orbofiban.

45. A pharmaceutical composition comprising a first amount of an aldosterone receptor antagonist, a second amount of an anti-obesity agent, and a pharmaceutically acceptable carrier, wherein the first amount of the aldosterone receptor antagonist and the second amount of the anti-obesity agent together comprise a therapeutically-effective amount of the aldosterone receptor antagonist and anti-obesity agent.

46. The composition of Claim 45 wherein the aldosterone receptor antagonist is selected from the group consisting of:

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ -lactone, methyl ester, (7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,(7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ -lactone, (6 β ,7 β ,11 β ,17 β)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt,(7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt, (7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, δ -actone(6 α ,7 α ,11 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6 α ,7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6 α ,7 α ,11 α ,17 α)-;

3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, δ -lactone, (6 α ,7 α ,11 α ,17 α)-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, δ -lactone, ethyl ester, (7 α ,11 α ,17 α)-; and

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, δ -lactone, 1-methylethyl ester, (7 α ,11 α ,17 α)-.

47. The composition of Claim 45 wherein the aldosterone receptor antagonist is eplerenone.

48. The composition of claim 47 wherein the eplerenone is administered in a daily dose range from about 1 to about 250 mg.

49. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of gastrointestinal lipase inhibitors, mixed norepinephrine and serotonin reuptake inhibitors, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

50. The composition of Claim 49 wherein the aldosterone receptor antagonist is eplerenone.

51. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of orlistat and sibutramine and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

52. The composition of Claim 51 wherein the aldosterone receptor antagonist is eplerenone.

53. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of a ciliary neurotrophic factor or one of its related variants or analogs; an appetite suppressant; a 5-HT-2c receptor agonist; a cannabinoid antagonist; a peptide or nonpeptide agonist of the cholecystokinin-A receptor; a peripherally acting agent that delays gastric emptying and increases satiety; an agonist of GLP-1 receptor; GLP-1s and related analogs, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

54. The composition of Claim 53 wherein the aldosterone receptor antagonist is eplerenone.

55. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of Axokine, CP-644673/P-57, BVT-933, Rimonabant/SR-141716, GI-181771, HMR-1426, and Exendin-4.

56. The composition of Claim 55 wherein the aldosterone receptor antagonist is

eplerenone.

57. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of human growth hormone fragments; PTP-1B inhibitors; DPP-IV inhibitors; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

58. The composition of Claim 57 wherein the aldosterone receptor antagonist is eplerenone.

59. The composition of Claim 45 wherein the anti-obesity agent is selected from the group consisting of neuropeptide Y1 antagonists; neuropeptide Y5 antagonists; thyroid hormone receptor beta agonists; glucocorticoid antagonists; melanocortin-4 receptor (MC-4) agonists; adiponectin/APM1/acrp30 and related analogs, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

60. The composition of Claim 59 wherein the aldosterone receptor antagonist is eplerenone.

61. The composition of Claim 45 the anti-obesity agent is selected from the group consisting of 11-beta-hydroxysteroid dehydrogenase-1 inhibitors; fatty acid synthase inhibitors; acetyl CoA carboxylase inhibitors; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

62. The composition of Claim 61 wherein the aldosterone receptor antagonist is eplerenone.

63. The composition of Claim 45 wherein the first amount of the aldosterone receptor antagonist produces no substantial diuretic or anti-hypertensive effect in a subject.

64. The composition of Claim 45 further comprising a third amount of a compound selected from the group consisting of anti-diabetic agents, renin inhibitors, angiotensin I

antagonists, angiotensin II antagonists, angiotensin converting enzyme inhibitors, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, calcium channel blockers, endothelin receptor antagonists, endothelin converting enzymes, vasodilators, diuretics, cyclooxygenase-2 inhibitors, apical sodium bile acid transport inhibitors, cholesterol absorption inhibitors, fibrates, niacin, statins, cholesteryl ester transfer protein inhibitors, bile acid sequestrants, anti-oxidants, vitamin E, probucol, IIb/IIIa antagonists, xemilofiban, and orbofiban.

65. A kit containing a first amount of an aldosterone receptor antagonist and a second amount of an anti-obesity agent.

66. The kit of Claim 65 comprising the first amount of the aldosterone receptor antagonist in a unit dosage form, and the second amount of an anti-obesity agent in a unit dosage form.

67. The kit of Claim 65 wherein the aldosterone receptor antagonist is eplerenone.

68. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of gastrointestinal lipase inhibitors, mixed norepinephrine and serotonin reuptake inhibitors, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

69. The kit of Claim 68 wherein the aldosterone receptor antagonist is eplerenone.

70. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of orlistat and sibutramine and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

71. The kit of Claim 70 wherein the aldosterone receptor antagonist is eplerenone.

72. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of a ciliary neurotrophic factor or one of its related variants or analogs; an appetite

suppressant; a 5-HT-2c receptor agonist; a cannabinoid antagonist; a peptide or nonpeptide agonist of the cholecystokinin-A receptor; a peripherally acting agent that delays gastric emptying and increases satiety; an agonist of GLP-1 receptor; GLP-1s and related analogs; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

73. The kit of Claim 72 wherein the aldosterone receptor antagonist is eplerenone.

74. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of Axokine, CP-644673/P-57, BVT-933, Rimonabant/SR-141716, GI-181771, HMR-1426, and Exendin-4.

75. The kit of Claim 74 wherein the aldosterone receptor antagonist is eplerenone.

76. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of human growth hormone fragments; PTP-1B inhibitors; DPP-IV inhibitors; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

77. The kit of Claim 76 wherein the aldosterone receptor antagonist is eplerenone.

78. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of neuropeptide Y1 antagonists; neuropeptide Y5 antagonists; thyroid hormone receptor beta agonists; glucocorticoid antagonists; melanocortin-4 receptor (MC-4) agonists; adiponectin/APM1/acrp30 and related analogs; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

79. The kit of Claim 78 wherein the aldosterone receptor antagonist is eplerenone.

80. The kit of Claim 65 the anti-obesity agent is selected from the group consisting of 11-beta-hydroxysteroid dehydrogenase-1 inhibitors; fatty acid synthase inhibitors; acetyl CoA carboxylase inhibitors; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

81. The kit of Claim 80 wherein the aldosterone receptor antagonist is eplerenone.

82. The kit of Claim 65 wherein the aldosterone receptor antagonist is spironolactone.

83. The kit of Claim 65 wherein the anti-obesity agent is selected from the group consisting of orlistat and sibutramine and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

84. The method of Claim 44 wherein the angiotensin converting enzyme inhibitor is selected from the group consisting of benazapril; captopril; cilazapril; enalapril; fosinopril; lisinopril; perindopril; quinopril; ramipril;trandolapril; and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

85. The method of Claim 84 wherein the anti-obesity agent is selected from the group consisting of orlistat and sibutramine, and the pharmaceutically acceptable salts, esters, conjugate acids, and prodrugs thereof.

86. The method of Claim 85 wherein the aldosterone receptor antagonist is eplerenone.

87. The method of claim 44 wherein the anti-diabetic agent is metformin.